REVIEW

Essential Fatty Acids, Lipid Membrane Abnormalities, and the Diagnosis and Treatment of Schizophrenia

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Recent research suggests that deficient uptake or excessive breakdown of membrane phospholipids may be associated with schizophrenia. We review available clinical research on abnormalities in membrane fatty acid composition and metabolism in schizophrenia, and therapeutic trials of fatty acid in this disorder.

All potentially relevant English-language articles were identified from the medical and psychiatric literature with the aid of computer searches using key words such as lipids, phospholipids, prostaglandins and schizophrenia. All studies which include human subjects are reviewed.

Empirical studies related to membrane hypotheses of schizophrenia focus on: 1) assessment of prostaglandins (PG) and their essential fatty acid (EFA) precursors in the tissues of patients with schizophrenia; 2) evaluation of the niacin flush test as a possible diagnostic marker; 3) evaluation of phospholipase enzyme activity; 4) NMR spectroscopy studies of brain phospholipid metabolism; and 5) therapeutic trials of PG precursors for the treatment of schizophrenia. The most consistent clinical findings include red blood cell fatty acid membrane abnormalities, NMR spectroscopy evidence of increased phospholipid turnover and a therapeutic effect of omega-3 fatty acid supplementation of neuroleptic treatment in some schizophrenia patients.

Studies of EFA metabolism have proved fruitful for generating and testing novel etiologic hypotheses and new therapeutic agents for schizophrenia. Greater attention to factors that influence tissue EFA levels such as diet, tobacco and alcohol are required to reconcile inconsistent findings. Treatment studies, although promising, require independent replication. Biol Psychiatry 2000;47: 8–21

Key Words: Schizophrenia, membrane physiology, essential fatty acids, psychopharmacology, treatment, phospholipids

Introduction

Identifying an effective, low cost, supplemental treatment with few side effects would be a major advance in schizophrenia therapeutics. In this context, recent reports of abnormalities in membrane phospholipid metabolism (Hudson et al 1996a, 1996b), an association between dietary fatty acid intake and prognosis in schizophrenia (Christensen and Christensen 1988) and the possibility that supplementation of neuroleptic treatment with essential fatty acids may improve clinical response (Puri and Richardson 1998; Peet and Mellor 1998) are intriguing. At present, even optimal modern pharmacologic treatment for schizophrenia leaves many patients with significant symptoms and disabilities; only 1 in 5, for example, recovers sufficiently to return to full-time work (Lehman 1995). Although augmentation of available antipsychotics is often attempted, no single agent or strategy has demonstrated clear superiority (Conley and Buchanan 1997). As a consequence, patients, families and clinicians remain keenly interested in exploring new therapeutic approaches.

What are fatty acids? Are tissue levels disrupted in schizophrenia? If so, what are possible biological causes and consequences of this disruption? Until recently, the evaluation of hypotheses relating to membrane lipid pathology in schizophrenia has not been in the mainstream of schizophrenia research (Rotrosen and Wolkin 1987; Mahadik et al 1994). Although innovative hypotheses have often been articulated (Horrobin 1998; McCreadie 1997; Gattaz and Brunner 1996), empirical clinical findings have been diverse, and to our knowledge, have not been comprehensively or critically reviewed.

In this article, we review clinical research on abnormalities in membrane fatty acid metabolism and therapeutic trials of fatty acid in schizophrenia. In addition, the biochemistry of membrane phospholipids is reviewed in sufficient detail to provide a rational framework for evaluating empirical findings.

Methods

This review is limited to studies of membrane fatty acids and fatty acid metabolism in schizophrenia. Abnormalities in phospholipids broadly (Rotrosen and Wolkin 1987), EFA use in dyskinesias (Vaddadi 1996), and studies of

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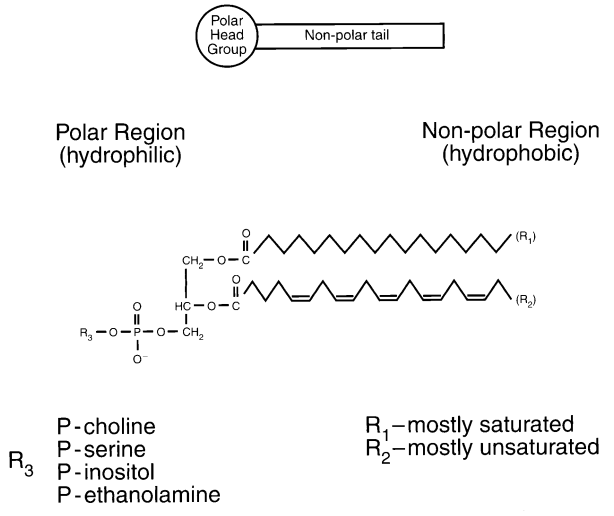

Figure 1. Generic chemical structure of membrane phospholipid.

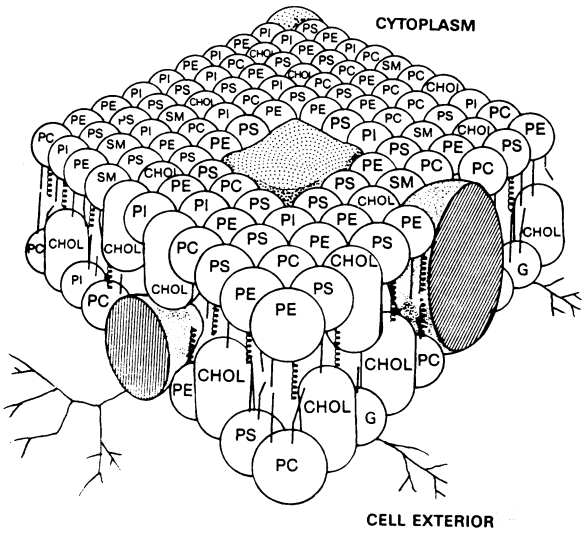

Figure 2. Schematic representation of phospholipid structure in plasma membranes. Saturated chains are indicated by a straight line, polyenes by a coil. CHOL, cholesterol molecules. The figure illustrates the preference of polyunsaturated fatty acids for the interior leaflet and the areas surrounding membrane proteins. (Reproduced with permission from Salem 1989a.)

oxidative membrane damage (Mahadik and Mukherjee 1996) have been reviewed elsewhere.

Potentially relevant English-language articles were identified from the psychiatric and psychological literature with the aid of computer searches using such key words as lipids, phospholipids, prostaglandins, essential fatty acids, treatment and schizophrenia. Bibliographies from primary sources and reviews were then used to identify earlier relevant works. All identified studies with human subjects with schizophrenia are included for review. Basic and preclinical investigations of potential relevance to understanding clinical findings are considered selectively. Insofar as clinicians may encounter patients taking supplemental omega-3 fatty acids, safety data for these compounds are also reviewed.

Background

Glycerophospholipids and cholesterol largely make up the membrane bilayer that form the matrix in which receptors, ion channels and other proteins involved in inter- and intra-cellular signal transduction are embedded. Glycerophospholipids include a phosphate-containing, hydrophilic head group and 2 acyl side chains (tail) derived from fatty acids. The specific hydrophilic head group varies and includes phosphatidyl (P)-ethanolamine, (P)-choline, (P)-serine, (P)-inositol. Hydrocarbon tails can range from 16 to 24 carbons; typically 1 chain is saturated (sn-1) and the second (sn-2) contains 1 or more double bonds (Figure 1) (Mathews and van Hold 1996). The double tailed structure yields roughly cylindrical molecules that can easily pack in parallel to form bilayer membranes. The hydrophilic head groups face outward toward the extracellular and intracellular spaces on either side of the hydrophobic inner area of the membrane. The degree of unsaturation (number of double bonds) in the long inward pointing hydrocarbon tails of these molecules determines the membrane order and fluidity. As represented in Figure 2, polyunsaturated chains are located preferentially on the inner leaflet of the membrane, and in areas surrounding membrane proteins.

Phospholipids, cholesterols, saturated fatty acids and monounsaturated fatty acids can be synthesized de novo within the human body. Because mammals cannot introduce a double bond beyond the delta-9 position in the fatty acid chain, however, linoleic (n-6) and linolenic acid (n-3) must be ingested in the diet. Each of these EFAs is in turn the substrate for further desaturation and elongation. The substrates and products comprise twelve essential fatty acids in 2 noninterchangeable series: **n-6** (linoleic (18:2n-6); gamma linolenic (18:3n-6); dihomogammalinolenic (DGLA) (20:3n-6); arachidonic (AA) (20:4n-6); adrenic (22:4n-6) and docosapentaenoic (DPA)(22:5n-6) and **n-3** (alpha-linolenic (ALA) (18:3n-3); strearidonic (18:4n-3); eicosatetraenoic (20:4 n-3); eicosapentanoic (EPA) (20:5n-3); docosapentaenoic (22:5n-3); docosahexaenoic (DHA) (22:6n-3) The **n-3** and **n-6** designation indicate that the third or sixth carbon bond respectively from the methyl end of the hydrocarbon chain is unsaturated. **N-3** and **n-6** nomenclature are synonymous with ω-3 (omega-3) and ω-6 (omega-6) (Figure 3). The numbers preceding the n-3 or n-6 designation indicate the total number of carbons (18 to 22) and total number of double bonds (2–5)

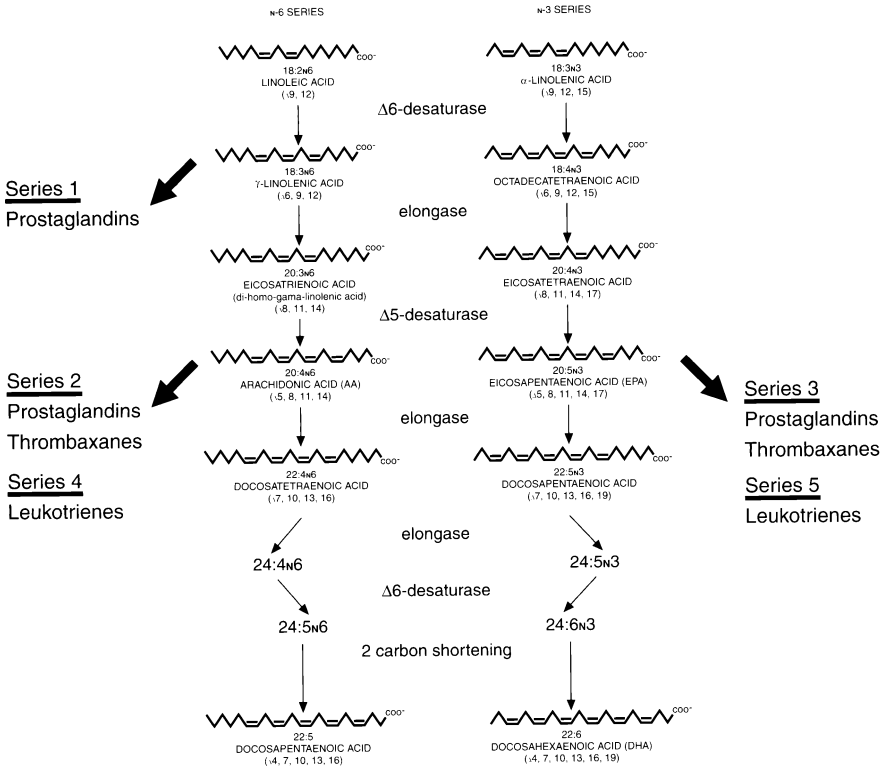

Figure 3. Metabolism of n-6 and n-3 essential fatty acids: these families of essential fatty acids cannot be interconverted.

in the fatty acid. Arachidonic acid (AA; 20:4n-6) and docosahexaenoic (DHA; 22:6n-3) are selectively concentrated in gray matter and together account for approximately 20% of the synaptosomal membrane fatty acid (Salem 1989a). These fatty acids, along with the prostaglandin precursors eicosapentaenoic (20:5n-3) and dihomogammalinolenic (DGLA; 20:3n-6) are most commonly studied and are designated by abbreviations AA, DHA, EPA and DGLA.

The specific EFA content of synaptic membrane can modify neuronal functioning and produce clinical effects through at least 2 mechanisms: first, changes in membrane EFA content alter the microenvironment and hence structure and function of membrane receptors, ion channels and enzymes; and second, EFAs contribute to cell regulation by acting as a source of precursors for second messengers in intra- and inter-cellular signal transduction.

Data from several sources indicate a significant role for membrane EFA as regulators of the activity of membrane proteins. Basic biochemical investigations provide many examples of protein functions that are modified by available concentration of DHA (Salem et al 1986; Salem and Niebylski 1995). Preclinical studies demonstrate that in addition to modulating the function of ion channels (Lundbaek and Anderson 1994), alterations in biophysical micro-environment of lipids and fatty acids modify agonist binding affinity for a wide range of neurotransmitter receptors including, among others, cholinergic (Fong and McNamee 1986), dopaminergic (Malnoe et al 1990), GABAergic (Witt and Nielsen 1994), and NMDA (Miller et al 1992) receptors. Furthermore, in rat models, changes in brain fatty acid concentrations induced by chronic dietary omega-3 fatty acid deficiency alters dopaminergic and serotonergic neurotransmission (Delion et al 1994) and induces an increase in 5-HT_2 and decrease in D_2 frontal cortex receptor density (Delion et al 1996). Impaired learning and behavioral performance is observed in omega-3 deficient rats (Salem and Ward 1993; Wainwright 1992; Yehuda 1997) and has been hypothesized to reflect changes in attention, motivation and reactivity consistent with a deficit in the function of prefrontal dopamine pathways (Reisbick and Neuringer 1997).

In addition to their role in maintaining membrane structure and modulating the function of membrane proteins, EFAs are the precursors of prostaglandins, thromboxanes and leukotrienes, collectively called eicosanoids. Among these are 1-series eicosanoids (derived from DGLA; 20:3n-6), 2-series eicosanoids (derived from AA; 20:4n-6) and 3-series eicosanoids (derived from EPA; 20:5n-3). DHA does not form biologically active stereospecific eicosanoids (Sawazaki et al 1994; Kim 1990) in brain tissue. Prostaglandins of the 1 (DGLA derived), 2

(AA derived) and 3 (EPA derived) series are synthesized after the release of fatty acids from membrane phospholipids, exert a short-acting local physiological effect and are rapidly metabolized. These eicosanoids mediate the acute phase response to infection (pain, fever, blood flow, clotting) and inhibition of their synthesis by PGH synthase and cyclooxygenase accounts for the clinical effect of aspirin and ibuprofen. Eicosanoids have a variety of other physiological and neurochemical effects and may serve as retrograde messengers in the processes underlying long-term changes in synaptic plasticity (Wainwright 1997).

EFA and eicosanoids also contribute to cellular regulatory function by acting as a source of second messengers in cellular signal transduction (Hudson et al 1993). Fatty acids can act as second messengers because their concentration is transiently altered when specific agonists bind to membrane receptors (Graber et al 1994). Membrane-bound polyunsaturated fatty acids become available as precursors for eicosanoid synthesis after activation of 1 or more cellular lipases, such as phospholipase A_2 or phospholipase C that cleaves fatty acid directly from membrane phospholipid (Mathews and van Hold 1996). Phospholipase C (PLC), for example, is activated through G protein coupled receptors and catalyzes the conversion of phosphatidylinositol biphosphate to diacylglycerol (DAG) and inositol triphosphate (IP_3). IP_3 releases calcium ions from intracellular stores that in the presence of DAG activates protein kinase C, a second messenger that regulates the activity of many neuronal proteins including those involved in gene expression (Wainwright 1997).

Membrane Hypothesis of Schizophrenia

The phospholipid membrane hypothesis of schizophrenia originates with suggestions by Feldberg (1976) and Horrobin (1977) that schizophrenia might be caused by a prostaglandin (PG) excess or deficiency. These proposals were based historical reports of a clinical association between fever and symptom remission in psychosis (Lipper and Werman 1977), the relative resistance to PG mediated pain and inflammation (Marchand et al 1969) and a reduced rate of rheumatoid arthritis in patients with schizophrenia (Melsop et al 1974), and the observation that PGE_1 injected into the CSF of mammals could induce catalepsy (Horrobin et al 1978).

Noting that PG are derived from membrane EFA, Horrobin (1977) hypothesized that defective phospholipase or cyclo-oxygenase function could lead to PG deficiency that might also be sensitive to dietary variations in EFA precursor availability. The observed failure of platelets of patients with schizophrenia to increase PGE1 production in response to ADP (Abdulla and Hamadah 1975) led Horrobin et al (1978) to further suggest that schizophrenia involved a failure to produce PGE_1 from EFA precursors. In addition, unlike normal controls, patients with schizophrenia reportedly did not demonstrate skin flushing (a PGE_1 mediated vasodilation) to an oral dose of 250 mg niacin (Horrobin 1980). Insofar as a physiological antagonism between PGE_1 and dopamine was posited, the PGE_1 deficiency theory was seen as complementary to neurotransmitter theories (Horrobin 1992).

Based, in part, on the observation of lowered levels of AA and DHA enriched phospholipids in cultured fibroblasts of chronic (Kelkar et al 1993) and first episode (Mahadik et al 1994) schizophrenia patients, recent modifications of the membrane phospholipid hypothesis have suggested 1) EFA depletion and cell injury that might result from excessive free radical generation or impaired anti-oxidant defense (Mahadik and Mukherjee 1996); 2) genetic variability in phospholipase mediated rate of EFA loss from cell membrane (Hudson et al 1996a); 3) defective uptake of EFAs into membrane phospholipids (Yao et al 1996; Horrobin 1998); or 4) defective conversion of EFAs into long-chain polyunsaturated analogs (EPA to DHA) as a result of lowered delta-4 desaturase activity (Mahadik et al 1996a, 1996b). Clinical studies derived from these hypotheses assess PG and EFA concentrations in the tissues of schizophrenia patients and attempt to reverse hypothesized deficiencies with EFA supplementation.

Clinical Studies

Empirical studies related to the membrane hypothesis have focused on 5 areas: 1) assessment of PG and their EFA precursors in the tissues (plasma, red blood cell [RBC] membrane, platelet, fibroblast, postmortem brain) of patients with schizophrenia; 2) evaluation of the niacin flush test as a possible diagnostic marker; 3) evaluation of phospholipase enzyme activity; 4) NMR spectroscopy studies of phospholipid metabolism; and 5) therapeutic trials of PGE1 or EFA precursors for the treatment of schizophrenia.

Prostaglandins

Mathe et al (1980) initially reported higher PGE_1 and PGE_2 concentrations in the CSF of 8 schizophrenic patients. Subsequent studies have been inconclusive: Gerner and Merrill (1983) found no difference in CSF PGE_1 and PGE_2 in patients compared to controls. Linnoila et al (1983) found elevated CSF PGE_2 in women with unipolar depression, but not schizophrenia patients; Kaiya et al (1989) reported significantly elevated PGE_2 in plasma of 40 schizophrenic patients compared to other psychiatric and normal controls. Advances in assay technology, that

now allow sensitive detection of individual prostaglandins, raise questions about the validity of all of these findings; no recent studies directly evaluate PG levels in schizophrenia. Absent a gross abnormality in metabolism, however, sensitive single cross-sectional PG measurements would most likely reflect transient fluctuations in immune response to endogenous or exogenous stress.

Tissue EFA Levels in Schizophrenia

Studies that assess EFA tissue levels in schizophrenia patients are summarized in Table 1. Depletion of linoleic (18:2n-6), AA (20:4n-6) and DHA (22:6n-3) in schizophrenia patients compared to controls has been most often replicated.

Primate studies suggest that RBC cell membrane EFA levels reflect frontal cortex EFA composition (Connor et al 1990). Depleted RBC membrane EFA is associated with altered measures of membrane dynamics and is found in both drug free and treated schizophrenia patients (Yao and van Kammen 1994; Yao et al 1994a, 1994b). A bimodal distribution of RBC EFA has been described in 3 samples (Peet et al 1994, 1995; Glen et al 1994; Horrobin 1992), and Glen et al (1994) found an association between negative symptoms and EFA depletion. Only 1 study fully evaluated diet, medication, alcohol, and tobacco use and reports no association between these factors and RBC membrane EFA (Doris et al 1998). Horrobin et al (1997), however, report an increase in membrane AA and DHA after clozapine treatment.

In the only study of EFA level in postmortem brain tissue, Horrobin et al (1991) found decreased 18 and 20 carbon EFA in frontal but not cerebellar cortex of 7 schizophrenia patients.

Niacin Challenge

In most normal subjects, oral niacin induces an increase in serum PGE_2 that results in vasodilatation through increased cAMP production (Lin and Hudson 1996). Horrobin (1980) first anecdotally reported that consistent with the prostaglandin deficiency hypothesis, 80% of schizophrenics failed to show a facial flushing to a oral dose of 250 mg niacin. Using objective measures of flush, Wilson and Douglass (1986) gave 16 schizophrenic patients and 18 controls niacin (3 mg/kg up to 200 mg) and found no objective evidence to support Horrobin's claim. Likewise, Fiedler et al (1986) using malar blood flow and cutaneous temperature as objective measures of skin flush, found no difference between 8 controls, 6 abstinent alcoholics and 9 schizophrenia patients after an IV infusion of 25 mg niacin. Relying on visual inspection and temperature measurement, Rybakowski and Weterle (1991) reported that 25/33 (76%) of patients with schizophrenia showed a flush response to 200 mg nicotinic acid compared to 18/18 100% of patients with endogenous depression. They suggested that a only a subpopulation of schizophrenia patients failed to show the flush response. Again suggesting subgroups, Hudson et al (1997) used thermocouple sensors to measure change in skin temperature relative to core body temperature in 28 schizophrenia patients, 18 patients with bipolar disorder, and 28 normal controls. In response to a 200 mg niacin challenge dose, 12/28 (43%) of schizophrenia patients, 1/18 (6%) bipolar patients, and none of 28 controls did not vasodilate. Glen et al (1996) administered 200 mg niacin to 92 patients with schizophrenia who later participated in a trial of evening primrose oil supplementation. Using visual inspection, 52/92 (59%) of patients did not flush. Among these patients, absence of flushing was significantly associated with low levels of RBC membrane AA (20:4n6) and DHA (22:6n3).

Ward et al (1998) recently described a topical test in which a variable concentration niacin containing strip is applied to the forearm and redness or edema is rated after 5 minutes on a 0–3 scale. The response of 38 schizophrenia patients was reportedly significantly less than that of 22 controls at all niacin concentrations.

Phospholipase A_2 Activity

Gattaz et al (1987) first reported significantly elevated phospholipase A_2 (PLA_2) activity in the plasma of 20 drug free schizophrenic patients compared to 6 nonschizophrenic psychiatric patients and 21 healthy controls. PLA_2 activity in schizophrenia decreased after neuroleptic treatment. In a replication study, Gattaz et al (1990) found elevated PLA_2 activity in serum of 14 drug free schizophrenic patients relative to 8 nonschizophrenia patients and 20 healthy controls. No difference was found in serum concentration of pancreatic PLA_2, suggesting that observed increases reflected specific intracellular PLA_2 activity. Noponen et al (1993) subsequently reported increased serum PLA_2 in both schizophrenic and nonschizophrenia psychiatric patients and Albers et al (1993) reported no difference in PLA_2 activity between 6 schizophrenic patients and 10 healthy controls. To directly evaluate intracellular PLA_2, Gattaz et al (1995) compared intracellular PLA_2 activity in platelets in 31 schizophrenia patients (15 drug naive), 31 age and gender matched other psychiatric patients and 31 matched normal controls. Platelet PLA_2 activity was significantly increased in schizophrenia patients compared to healthy and psychiatric controls and neuroleptic treatment reduced enzyme activity. The findings were described as consistent with accelerated breakdown of membrane phospholipids in schizophrenia.

Ross et al (1997) used 2 analytic techniques (fluorometric and radiometric) to measure serum PLA_2 in 24 neuro-

Table 1. EFA Studies in Schizophrenia Patients

Study	Nationality	N	18:2N6	18:3N6	20:3N6	20:4N6	22:4N6	22:5N6	18:3N3	18:4N3	20:4N3	20:5N3	22:5N3	22:6N3
RBC membrane														
Obi and Nwanze 1979	Nigeria	6							↑					
Vaddadi et al 1986	Scotland	16	↓	↑		↓	↓						↓	↑
Vaddadi et al 1989	UK	17				↓	↓						↓	↓
Yao et al 1994	US	24	↓			↓								
Peet et al 1995	UK	23	↓			↓						↓		↓
Glen et al 1994	UK	13[a]	↓		↓	↓						↓		↓
Vaddadi et al 1996	Australia	72	↓										↑	
Doris et al 1998	Scotland	40			↑									
Plasma														
Obi and Nwanzi 1979	Nigeria	6												
Horrobin et al 1989	UK, Ireland, Scotland	61	↓			↓								
Kaiya et al 1991	Japan	59	↓		↑								↑	
Bates et al 1991	US	38		↑	↑		↑	↑						↓
Thrombocytes														
Fisher et al 1992	Germany	16	↓						↓			↓		↓
Cultured fibroblast														
Mahadik et al 1996a	US	12												↓
Brain (postmortem)														
Horrobin et al 1991	Scotland	7	↓			↓								↓

[a]Compared to positive-symptom patients.

leptic treated patients with schizophrenia, and age and gender matched controls. Using the fluorometric procedure as used by Gattaz (1990) PLA_2 activity was significantly increased in patients with schizophrenia. Using radiometric assay, as used by Albers et al (1993) no difference was noted. Further analysis indicated the 2 methods assayed distinct calcium-sensitive and independent enzymes, and only increased activity of the latter was elevated in schizophrenia.

Hudson et al (1996a, 1996b) conducted preliminary association and haplotype relative risk studies to assess a possible genetic basis for altered PLA_2 activity in schizophrenia. Polymorphisms in the region of the genome of $cPLA_2$ on chromosome 1 were studied in 65 patients with schizophrenia and 65 matched healthy controls. An increased of alleles 7–10 near the $cPLA_2$ promoter region and a reduced presence of alleles 1–6 was reported among schizophrenia patients in the association study. The study of 44 nuclear families typed for $cPLA_2$ poly A polymorphism also revealed an association between distribution of allele frequencies with a significant increase in allele frequency for A8 in individuals with schizophrenia. In an independent sample, however, Doris et al (1998) failed to replicate the finding of an allelic association between a polymorphism close to the site of the cytosolic phospholipase A_2 gene and schizophrenia.

NMR Spectroscopy

Pettegrew et al (1991) first used phosphorus 31 (p31) NMR spectroscopy to directly assess in vivo brain membrane phospholipid metabolism. When 11 drug naive first episode schizophrenia patients were compared to 10 matched healthy control volunteers, schizophrenia patients had significantly reduced levels of phosphomonoesters (PME) and increased phosphodiesters (PDE) in dorsal prefrontal cortex. PME are precursors to phospholipid membrane synthesis and PDE membrane phospholipid breakdown products. Findings were interpreted as consistent with decreased synthesis and increased breakdown of membrane phospholipids, analogous to premature brain aging in early schizophrenia (Pettegrew et al 1993). Using p31 MR spectroscopy Williamson et al (1991) reported lower PME levels but no differences in PDE in the left dorsolateral prefrontal area in 10 medicated chronic schizophrenia patients compared to 7 controls. Stanley et al (1994) also reported significantly decreased PME levels in prefrontal cortex among 19 medicated schizophrenia patients compared to 18 matched controls. Increased PDE levels (breakdown products of membrane phospholipids) were seen only in a newly diagnosed patient subgroup. In a second p31 NMR spectroscopy study, Stanley et al (1995) examined phospholipid metabolism in 11 drug naive, 8 newly diagnosed medicated, and 10 chronic medicated schizophrenia patients with age and gender matched controls. Decreased levels of PME were found in drug naive, newly diagnosed medicated and chronic medicated patients. Increased PDE was found in drug naive patients. Thus a reduction in precursors of membrane phospholipid (PME) was seen at all illness phases, but increased breakdown products (PDE) at early stage illness before medication treatment. Suggesting anatomic, but not illness stage specificity, Deicken et al (1994) reported higher PDE in the frontal but not parietal lobes in 20 chronic schizophrenia patients compared to 16 matched controls. Other p31 NMR spectroscopy studies have reported correlations between lowered frontal PME levels and negative symptoms (Shioiri et al 1994) and Wisconsin Card Sort Performance (Deicken et al 1995) in patients with schizophrenia.

EFA/Absorption and Metabolism

Free fatty acids are rapidly and completely absorbed. Large chain fatty acids are normally more than 99% bound to serum proteins. Protein binding is accompanied by a rapid dissociation rate and rapid exchange between the brain and blood of unbound and unincorporated EFA. As a result, the uptake by the brain of free fatty acids is rapid, buffered against short-term fluctuations in blood levels, and primarily reflects the metabolic needs of the brain (Banks et al 1997).

Tissue levels of n-3 fatty acids reflect dietary intake; studies of normal volunteers receiving EPA and DHA supplementation (0.5–15 g/d) have shown significant increases in n-3 fatty acids and decreases in n-6 FA in plasma, lipid fractions, in platelets and in erythrocyte membranes over 2–3 months (Vidgren et al 1997; Prisco et al 1996). Longer term study of kinetics of incorporation suggest that EFA levels in cholesteryl esters reflect intake over the past week or two, erythrocytes over the past month or two and adipose tissue over a period of years (Katan et al 1997).

Incorporation of dietary fatty acids into brain is of concern in infant formula development. A study of male rats suggests rapid incorporation of dietary EFA in brain, retina and sciatic nerve membrane phospholipid over a 5 week feeding trial (Philbrick et al 1987). A study of the metabolism of individual dietary n-3 fatty acids in deficient newly hatched chicks indicated that ingested EPA or DHA reversed deficiencies in brain and retina DHA by Week 3 (Anderson et al 1990). To our knowledge, in vivo PET studies of DHA incorporation have not been conducted in humans. A normalization of deficient DHA levels and normalization of MRI brain myelin images after oral treatment with ethyl DHA, however, has been re-

Table 2. Clinical Trials of Omega-6 and Omega-3 Fatty Acid Supplementation in Schizophrenia

Omega-6 Studies				
Study	Holman and Bell 1983	Vaddadi et al 1986	Vaddadi et al 1989	Wolkin et al 1996
Design	Double blind	Double blind 3-arm	Double blind	Double blind
n	10	21	48	16
Treatment	Efamol 4 g (γ-lenolenic)	(1) DGLA 1 g and neuroleptic (2) DGLA plus placebo (3) Placebo only	Efamol 12 caps qd	Efamol 600 mg qd
Duration	16 weeks	12 weeks	8 months	6 weeks
Efficacy measures	BPRS	BPRS	CPRS	BPRS
Baseline score	29	(1) 37.4 (2) 31.8 (3) 39.0	12.2	46
Best treatment score	7	(1) 27.8 (2) 21.2 (3) 35.7	8.5	45
% Change active	NS	(1) 26% (2) 33% NS	30%	NS
% Change placebo	NS	(3) 8.5%	7% (liquid paraffin)	NS

Omega-3 Studies				
Study	Mellor et al 1995 Peet et al 1996	Shah et al 1998	Puri and Richardson 1998	Peet and Mellor 1998
Design	Open	Open	Single case	Double blind 3-arm
n	20	10	One	45
Treatment	maxEPA 10 g	Kirunal (EPA) 2 g	EPA	(1) EPA (2) DHA (3) Linoleic
Duration	6 weeks	3 months	6 months	?
Efficacy measures	PANSS	PANSS	SAPS/SANS	PANSS
Baseline score	78.9	75.3	46/16	?
Best treatment score	65.6	46.5	7/3	?
% Change active	17%	29%	85%/89%	23.8% EPA (positive symptoms only) 3.3% DHA
% Change placebo	NA	NA	NA	13.7% (linoleic)

ported in a small series of young patients with generalized peroxisomal disorders (Martinez and Vazquez 1998).

Safety and General Health Effects of EFA Supplementation

Omega-3 fatty acids are designated GRAS (Generally Regarded as Safe) provided that daily intakes of DHA and EPA from menhaden oil do not exceed 3 grams per day (Department of Health and Human Services 1997). General medical effects of fish oil supplements rich in omega-3 fatty acids have recently been reviewed (Drug Therapy Bulletin, 1996). Interest in fish oils is based on the observation that death from coronary artery disease (CAD) is rare among Inuit population of the Arctic who have reduced platelet aggregation and a prolonged bleeding time, due to a diet rich in EPA and DHA. Epidemiologic studies demonstrate an association between fish consumption and decreased risk of CAD. Clinical studies report decreased risk of first heart attack, decreased death from heart disease after MI and a lower frequency of restenosis after angioplasty with omega-3 fatty acid supplementation. In patients with severe hypertriglyceridemia, omega-3 fish oil supplement reduces plasma triglycerides, its only licensed indication in the UK.

Fish oil supplements can cause belching and mild nausea, exacerbation of asthma in aspirin-sensitive patients and in high doses a rise in glucose in non–insulin dependent diabetes. Because of increased bleeding times, caution is recommended if fish oil is used in hemophiliacs or anyone taking high doses of anticoagulants or aspirin.

Treatment Studies in Schizophrenia

Membrane EFA or PG deficiency hypotheses have provided the rationale for attempts to treat symptoms of schizophrenia with omega-6, omega-3 fatty acids and PGE_1. Open-label or double-blind clinical trials and case reports that assess supplementation of neuroleptic treatment are summarized in Table 2.

Omega-6 Trials

Three of 4 small double-blind trials of omega-6 fatty acid supplementation of neuroleptic medication have yielded negative results. After preliminary case reports (Vaddadi

1979; Vaddadi et al 1986) randomly assigned 21 long stay treatment resistant schizophrenia inpatients to 1 of 3 treatment groups in a 3 month prospective randomized trial: 1) depot phenothiazine and 1 gm DGLA (20:3n-6); 2) placebo depot injections and 1 gm DGLA (20:2n-6) acid; and 3) placebo injections and placebo capsules. At 3 months no significant difference across groups was noted, but tardive dyskinesia was described as improved in 2 patients who received DGLA. In a second placebo controlled crossover study, Vaddadi et al (1989) treated 48 patients with tardive dyskinesia in a double blind trial of Efamol (mostly linoleic acid [18:2n-6], 405 mg daily) supplementation over 8 months. In this study, no effect of supplementation on tardive dyskinesia was found, but Efamol treated patients showed a significant improvement in symptoms and Weschsler memory quotient that reversed at crossover. Two independent, double-blind, placebo-controlled replication attempts, however, were negative (Holman and Bell 1983; Wolkin et al 1986).

Omega-3 Trials

In contrast to omega-6 trials, all published studies of omega-3 EFA treatment report positive results. Rudin (1981) initially provided case reports of 3 patients with relapsing schizophrenia who improved after supplementation with omega-3 rich linseed oil. In an open study, Mellor et al (Mellor et al 1995; Peet et al 1996) supplemented 20 hospitalized patients with chronic schizophrenia with 10 grams maxEPA fish oil daily for 6 weeks. Over the trial, a 17% improvement in PANSS symptom ratings and 40% improvement in AIMS scores were noted. At intake, patients reporting greater dietary n-3 consumption were significantly less symptomatic and improvement during the trial was significantly associated with an increase in RBC membrane n-3 concentration. Puri and Richardson (1998) described a single case of a 31-year-old drug-free patient with longstanding schizophrenia who demonstrated an 85–80% improvement in SAPS/SANS scores over the course of 6 months treatment with EPA (n-3) 2 grams daily. Shah et al (1998) treated 10 neuroleptic treated schizophrenic patients with significant residual symptoms with EPA 2 grams (*Kirunal*) daily for 3 months. A 29% decrease in PANSS score was reported. In a preliminary report from a double-blind, placebo-controlled augmentation trial of an EPA enriched oil, DHA enriched oil and placebo among 45 neuroleptic treated patients, Peet and Mellor (1998) reported a 24% improvement in PANSS among EPA treated patients, 3% improvement in DHA treated patients and 14% improvement among linoleic treated control patients. A full report of this trial is not yet available.

Prostaglandin E_1

Kaiya (1984) and colleagues (Kaiya et al 1985) intravenously administered prostaglandin E_1 for 8 to 21 days to 7 unmedicated patients with acute schizophrenic symptoms. Two patients were described as responding (4 showing transient improvement, and 1 no effect). Minimal side effects were noted.

Discussion

Empirical findings concerning essential fatty acid and lipid membrane abnormalities and efforts to treat schizophrenia with fatty acids derive from a diverse set of investigations conducted over more than 2 decades. In each of the 5 areas that have been subject to empirical study, intriguing, but inconclusive and at times contradictory results are apparent.

Little empirical data support the hypothesis that a simple prostaglandin deficiency is related to schizophrenia. At the same time, depletion of particular EFA PG precursors in the tissue of schizophrenia patients has been replicated in several studies. Decreased concentrations of RBC membrane AA (20:4n-6), and DHA (22:6n3) are reported in 3 or more studies and 3 investigations suggest bimodality in distribution of these EFA in patients, but not controls. Interpretation of these abnormalities, however, is limited by a lack of specific knowledge about the relationship between human brain and RBC fatty acid concentrations (Keshavan et al 1993). In addition, smoking, stress, alcohol intake and diet may each be factors that confound patient-control comparisons. Because most studies have neither measured nor controlled for these factors, we can not be certain whether observed differences are primary to the illness or secondary. The interpretation of differences in tissue EFA levels in patients and controls is also complicated by simultaneous measurement of 12 essential fatty acids that is likely to yield spurious statistical findings due to multiple hypothesis testing (Grove and Andreasen 1982).

Although anecdotal reports claim specificity of the niacin challenge as an indicator of schizophrenia, empirical investigations indicate that only a subgroup (24–59%) of schizophrenia patients fail to have the expected flush. Thus, the niacin flush cannot be a sensitive diagnostic indicator for schizophrenia broadly. Studies conducted to date have differed in dose of niacin, route of administration, and methodology used to assess flush. As is true for studies of EFA tissue concentrations, the potentially confounding influence of factors such smoking, alcohol, and medications have not been evaluated. Further studies with larger samples of patients, non-patient controls, and individuals with other disorders are required to understand the

clinical or pathological significance of this abnormality in a yet incompletely characterized subgroup of patients.

Depleted tissue EFA may be a product of 1) altered dietary intake; 2) decreased metabolism; 3) excessive peroxidation due to exogenous (alcohol, tobacco) factors; or 4) excessive peroxidation due to genetic variability in enzyme activity. Although 4 studies (Gattaz et al 1987; Gattaz et al 1990; Noponen et al 1993, Ross et al 1997) report elevated phospholipase A_2 activity in schizophrenic patients compared to controls, differentiating among multiple potential tissue sources of circulating PLA_2 is problematic (Ross et al 1997). Due to the large number of cell-specific PLA_2 variants (Murakami et al 1997) we cannot conclude that currently available peripheral measures of secretory PLA_2s reflect central activity. Reports of an allelic association between a polymorphism close to the site of the cytosolic phospholipase A_2 gene (Hudson 1996a) have not been replicated (Doris et al 1998).

The most consistent evidence of membrane phospholipid abnormalities in schizophrenia derive from 4 NMR studies indicating reduced membrane phospholipid precursors (Pettegrew 1991; Williamson et al 1991; Stanley et al 1994; Stanley et al 1995) in patients compared to controls. Further, the finding of elevated breakdown products only at early illness stages in 1 study (Stanley et al 1994) is of particularly interest in relation to theories of illness onset and pathophysiologic progression that postulate excessive pruning or aberrant synaptic modeling (Hoffman and McGlashan 1997). Repeated measures in patients identified early in the illness and followed prospectively would be of particular value in evaluating these hypotheses.

Membrane phospholipid hypotheses are appealing because of their apparent ability to account for a range of disparate findings related to schizophrenia. As outlined by Horrobin in an inventive series of hypothesis generating reviews these include: a relative resistance to pain and inflammation among some schizophrenic patients (Horrobin 1977; Davis et al 1979) and negative association between schizophrenia and inflammatory disease such as rheumatoid arthritis (Vinogradov et al 1991); reports of transient remission of psychosis with fever (Horrobin et al 1978; Lipper and Werman 1977); evidence of both genetic and environmental (in utero exposure to starvation, viral infection) contributions to risk (Horrobin 1992, 1999), an association between dietary unsaturated fat consumption and outcome of psychosis in multinational World Health Organization follow-up study of schizophrenia (Christensen and Christensen 1988); and a possible association between formula feeding and risk of schizophrenia (McCreadie 1997). Further, phospholipid hypotheses are consistent with both dysfunction of multiple neurotransmitter systems and neurodevelopmental abnormalities associated with aberrant cell migration or remodeling (Horrobin 1998).

Although membrane lipid hypotheses have considerable heuristic appeal, their ability to link multiple observations about schizophrenia may also reflect a major weakness of these theories. Phospholipids and essential fatty acids are so ubiquitous in the central nervous system that their metabolism is only 1 or 2 steps removed from many neurobiological processes. Thus, abnormalities in fatty acid metabolism are not specific to schizophrenia and have been reported in range of conditions including depression (Hibbeln and Salem 1995; Maes and Smith 1998), alcoholism (Salem 1989b), movement disorders (Nilsson et al 1996) retinitis pigmentosa (Bazen 1990) and generalized peroxisomal disorders (Martinez and Vazquez 1998).

The ultimate value of lipid membrane hypotheses, however, rests in the possibility of opening avenues to novel therapeutic approaches. Two small open trials (Mellor et al 1995; Shah et al 1998), a case report (Puri and Richardson 1998), and a single double-blind trial (Peet 1998) suggest supplementation with omega-3 (eicosapentaenoic acid) may improve residual symptoms when added to standard neuroleptic treatment. Supporting an eicosanoid related mechanism of action, DHA did not show a significant therapeutic effect relative to placebo (Peet and Mellor 1998). Further carefully designed, randomized clinical trials to evaluate the therapeutic potential of these low cost and nontoxic agents should be conducted. Independent replication confirming a significant benefit of EPA supplementation will trigger a major effort to understand its pathophysiologic significance and mechanism of action in schizophrenia.

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